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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/648,843	08/26/2003	Charles Huang	690068.587C1	3857

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EXAMINER	
TRUONG, TAMTHOM NGO	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 08/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/648,843	HUANG ET AL.	
	Examiner	Art Unit	
	Tamthom N. Truong	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2-6-06*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6,7 and 13-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,7 and 13-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

NON-FINAL ACTION

Applicant's amendment of 2-6-06 has been fully considered.

The cancellation of claims 5 and 8-12 have overcome the previous rejections of 112/2nd paragraph, 101 and Statutory Double Patenting. Thus, said rejections are now withdrawn.

The Terminal Disclaimer has also overcome the previous rejection of Obviousness-type Double Patenting, and so, said rejection is now withdrawn.

Applicant's argument has also overcome the previous 102 rejection.

Claims 1-4, 6, 7 and 13-16 are pending.

The following issue of enablement is noted and presented below.

Specification

1. The specification is objected for the following inconsistency:

The preparation of compound (19) refers to Example B-3 (specifically, intermediate (5)). However, intermediate (5) is a quinoline which cannot yield a quinazoline compound such as compound (19).

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. **Scope of Enablement:** Claims 1-4, 6, 7 and 13-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the preparation and use of **quinoline** compounds, does not reasonably provide enablement for the preparation and use of **quinazoline** compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in the determination of an enabling disclosure:

(1) The breadth of the claims;

(2) The amount of direction or guidance presented;

(3) The state of the prior art;

(4) The relative skill of those in the art;

(5) The predictability or unpredictability of the art;

(6) The quantity of experimentation necessary;

[See ***Ex parte Forman***, 230 USPQ 546 (Bd. Pat. App. & Int., 1986); also ***In re Wands***, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)].

The breadth of the claims: Claim 1 recites formula (I) which encompasses *quinoline* and *quinazoline* compounds which are substituted with groups represented by R^1-R^5. Thus, formula (I) essentially includes two Markush groups, each of which requires a separate process

of making as well as having different biological activities. Thus, the scope of claim 1 is unduly broad.

Claims 2-4, 6, 7 and 13-16 depend on claim 1 and recite both quinoline and quinazoline compounds, and thus they also have unduly broad scope.

The guidance provided: As mention in the objection above, the specification refers to Example B3 for the preparation of quinazoline compounds. However, said example has intermediate (5) which is a quinoline compound. Thus, following Example B-3, no quinazoline compound can be obtained. Regarding biological activity, only compound (6) is tested; however, compound (6) is a quinazoline substituted with a ***halogen*** at the position of R^3. Therefore, compound (6) is not a good representative of quinazoline group in formula (I) which requires R^3 to always be a ***ring***. With the inconsistency in the specification, there is no sufficient enablement to guide the skilled chemist in making or using a quinazoline compound as recited in the claims above.

The state of the prior art: As evident by the teaching of **Selby** (US'347 – cited previously), a quinoline compound substituted with a ring at the position of R^3 can be prepared. However, even those compounds are not known to antagonize CRF receptor, let alone a quinazoline compound. Thus, the state of the prior art does not support the broad scope formula (I) for both quinoline and quinazoline compounds.

The relative skill of those in the art: Even with the advanced training, the skilled clinician would have to carry out extensive research to select an effective compound from the large Markush group of formula I. Not only one has to determine an IC_{50} value, but also *in-vivo*

activity to establish an LD_{50}, therapeutic index and pharmacokinetic profile for each compound. Given a large Markush group of the claimed formula I, such a task would require a tremendous amount of effort, time and resource.

The predictability or unpredictability of the art & The quantity of experimentation necessary: The pharmaceutical art has been known for its unpredictability due to various conflicting pathways, or biological factors that are sometimes genetically unique to individuals. In the instant case, the specification does not provide starting materials for making quinazoline compounds of formula I. It also fails to provide biological data for using the claimed quinazoline compounds in a method of antagonizing CRF receptor. Thus, with the large Markush group of formula I, without the guidance for starting material sources to make quinazoline compounds, undue experimentation is necessary for making such an array of compounds as well as establishing biological activity for those compounds as antagonists of CRF receptor.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. **Scope of Enablement:** Claims 13-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of *depression*, does not reasonably provide enablement for the treatment of other diseases related to CRF receptor such

as: *an anxiety-related disorder, a feeding disorder, stress-induced immune suppression, stroke, Cushing's disease, infantile spasms, epilepsy, seizure, and an inflammatory condition.* The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The breadth of the claims: Claim 13 recites: "A method of antagonizind a CRF receptor..." which includes:

Claim 14 recites: "A method of treating a disorder manifesting hypersecretion of CRF..." which basically covers the treatment of an array of disorders recited in claim 13.

Claim 15 recites the treatment of a number of disorders of various underlying factors and manifestation. Note, the term "anxiety-related disorder" covers more than anxiety. It includes some GI disorder (e.g., acid hypersecretion), pain, headache, insomnia, etc. Likewise, the term "inflammatory condition" covers asthma, allergy, arthritis, etc.

Claim 16 depends on claim 15, and recites only the treatment of feeding disorder and irritable bowel syndrome.

The guidance provided: The specification only describes the "CRF Recepor Binding Assay". A handful of compounds were tested, which had a general K_i value of ≤ 250 nM. None of the claimed compounds was tested *in-vivo*. There is no evidence if any of the claimed compounds could increase appetite for treating anorexia or bulimia, inhibit convulsion for treating seizure, reduce swelling for treating inflammatory condition. Likewise, there is no evidence for the treatment of stroke, Cushing's disease, anxiety, etc.

The state of prior art: The antagonizing of CRF receptor is known in the art for treating depression. However, for other disorders, there is no substantial correlation. For example, there is no available drug that could treat an inflammatory condition and a feeding disorder. Drugs that treat inflammatory condition often adverrsly affect the GI system, and thus would likely be contraindicated in treating feeding disorder (e.g., bulimia). Thus, the state of the prior art does not support the claimed method of treatment.

The relative skill of those in the art: Even with the advanced training, the skilled clinician would have to carry out extensive research to select an effective compound from the large Markush group of formula I. Not only one has to determine an IC_{50} value, but also *in-vivo* activity to establish an LD_{50}, therapeutic index and pharmacokinetic profile for each compound in each indication. Given a large Markush group of the claimed formula I, such a task would require a tremendous amount of effort, time and resource.

The predictability or unpredictability of the art & The quantity of experimentation necessary: The pharmaceutical art has been known for its unpredictability due to various conflicting pathways, or biological factors that are sometimes genetically unique to individuals. In the instant case the specification only provides one *in-vitro* assay for CRF binding activity with only a handful of compounds tested. The K_i value was disclosed as a general value of $\leq$ 250 nM. Such a guidance does not sufficiently guide the skilled clinician in selecting an effective compound to treat various diseases or disorders that are allegedly related to CRF receptor.

See ***Hoffman v. Klaus*** 9 USPQ 2d 1657, and ***Ex parte Powers*** 220 USPQ 925 regarding type of testing needed to support *in vivo* uses.

Note, the "how to use" requirements of 35 USC 112 are not met by disclosing only a pharmacological activity of the claimed compound if one skilled in the art would not be able to use the compound effectively without undue experimentation. See **In re Diedrich**, 138 USPQ 128; **In re Gardner et. al.**, 166 USPQ 138. Thus, where claimed compounds do not bear structures that are similar to known compounds having the same activity and their pharmaceutical properties could not be predicted from their chemical structure, a disclosure that they possess a particular activity may not suffice as a description of how to use as required by 35 USC 112. See **In re Moureu et. al.** 145 USPQ 452. Note, the Federal Circuit has repeatedly held that "the specification must teach those skilled in the art how to make and use the **full scope** of the invention without 'undue experimentation'".

Thus, given the unpredictable nature of the art, and the vast number of compounds claimed herein, one skilled in the art will have to carry out undue experimentation to practice the method of treatment recited in claims 13-16.

No pending claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tamthom N. Truong whose telephone number is 571-272-0676. The examiner can normally be reached on M, T and Th (9:00-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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7-27-06

Tamthom N. Truong
Examiner
Art Unit 1624

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